Received: 31 August 2020 | Revised: 8 October 2020 | Accepted: 10 October 2020

DOI: 10.1111/dth.14419

DERMATOLOGIC THERAPY WILEY

LETTER

Promoting wound healing of uremic calciphylaxis leg ulcers using topical cannabis-based medicines

Dear Editor,

Calciphylaxis is a rare vasculopathy that mostly occurs in the chronic renal failure population.[1,2] Most commonly referred to as Uremic Calciphylaxis (UC), it may also be dubbed Calcific Uremic Arteriolopathy.[1,2] UC is a vexing, enigmatic, and often lethal complication afflicting patients with chronic renal failure.[1,2] UC occurs in about 1% in individuals with chronic renal failure. Integumentary lesions caused by calciphylaxis are associated with significant tissue necrosis and thus predispose to deep space infection and sepsis.[1,2] Integumentary wounds caused by calciphylaxis are among the most painful wound types and thus negatively impact on a patient's quality of life, functional capacities, and dignity. The 1-year mortality rate in patients with calciphylaxis associated with UC has been reported at an alarming 45% to 80%, with sepsis being the leading cause of death.[2]

There is no effective standard treatment for UC leg ulcers, and thus, healing rates are dismal. A recent systematic review in UC found no significant clinical benefit from the five most frequently used treatment modalities: sodium thiosulfate, parathyroidectomy, cinacalcet, hyperbaric oxygen, and bisphosphates.[3] It is important to note that all the aforementioned treatments are systemic, invasive (intravenous and/or intralesional injections), and associated with significant side effect burden and high financial costs.[3]

The endocannabinoid system (ECS) is a chemical signaling system that holds a ubiquitous presence in all organ systems among mammalian species.[4] Furthermore, the ECS is embodied throughout all levels, components, and appendages of the integumentary system, both cutaneous and mucous membranes.[4-7] ECS signaling goes beyond the classic cannabinoid receptors, CB_1 and CB_2, by involving other extracellular receptors such as TRPV, GPR, and 5-HT, as well as acting on nuclear receptors such as PPAR.[5] It has been theorized that dysregulated ECS signaling is central to the pathophysiology of integumentary and wound conditions.[4-7]

Our multi-cohort open label clinical trial (ISRCTN16488940) treated 33 patients with high levels of co-morbid illness afflicted with intractable non-healing wounds. Proprietary cannabis-based medicines applied topically to both wound beds and peri-wound tissues demonstrated promotion of wound closure in up to 90% of cases. The overall clinical trial contained only one patient with uremic calciphylaxis. We have published our results using Topical Cannabis-Based Medicines (Table 1), VS-12 to wound beds and VS-14 to peri-wound tissues, in a cohort of patients with non-uremic calciphylaxis leg ulcers.[8]

A 74-year-old woman with bilateral leg ulcers of more than 12-month duration was treated with Topical Cannabis-Based Medicines, VS-12 and VS-14. She was extremely frail, sarcopenic, and suffered from end-stage cardiac failure and peripheral vascular disease while undergoing hemodialysis for end-stage diabetic nephropathy; her palliative performance scale score was 50% (healthy persons score 100%) and M3 multimorbidity index was 4.79 (two thirds of persons from typical populations score zero). During her treatment course, her average hemoglobin was 91 g/L and her oxygen saturation was consistently <90%. She presented with large necrotic wounds involving both legs that were debrided; biopsies confirmed the diagnosis of UC. She had medical contraindications to other available experimental treatments. Our protocol involved daily application of TCBM, VS-12 to the wound beds, and VS-14 to a 4 to 6 cm radial cuff of peri-wound integument. Tissues were then covered with one layer each of Jelonet and Mesorb, followed by spiral bandaging of her lower limbs, sequentially, using gauze kling roll, Comprilan, and Easifix. Unfortunately, her tri-weekly dialysis sessions limited her to only 11 TCBM treatments over 21 days.

Representative digital images were acquired on day 0, 7, and 21, before the patient passed away from her cardiac conditions. Retrospective review of photographs using planimetric image analysis[9]

TABLE 1 Specifications of VS-12 and VS-14

Components	VS-12 applied to wound bed	VS-14 applied to peri-wound
Base carrier	Hyaluronic acid + *Aloe Vera* Gel 1/1 v/v	Liposomal base[a]
CBD	3.75 mg/ml	3.75 mg/ml
THC	<1 mg/ml	<1 mg/ml
Quercetin	31.25 mg/ml	31.25 mg/ml
Diosmin	25.31 mg/ml	25.31 mg/ml
Hesperidin	2.5 mg/ml	2.5 mg/ml
Beta carophyllene	152.69 mg/ml	152.69 mg/ml

Abbreviations: CBD, cannabidiol; THC, delta-9 tetrahydrocannabinol.
[a]Promotes penetration of cannabinoids, terpenes, and flavonoids through stratum corneum and into peri-wound tissues.

List of Abbreviations: 5-HT, 5-Hydroxytryptamine Receptor; CB_1, Cannabinoid Receptor 1; CB_2, Cannabinoid Receptor 2; CBD, Cannabidiol; ECS, Endocannabinoid System; GPR, G Protein-Coupled Receptor; PPAR, Peroxisome Proliferator-Activated Receptor; TCBM, Topical Cannabis-Based Medicines; THC, Delta-9-Tetrahydrocannabinol; TRPV, Transient Receptor Potential Cation Channel Subfamily V; UC, Uremic Calciphylaxis; VS-12, VinSan formula 12 for wound beds; VS-14, VinSan formula 14 for peri-wound tissues.

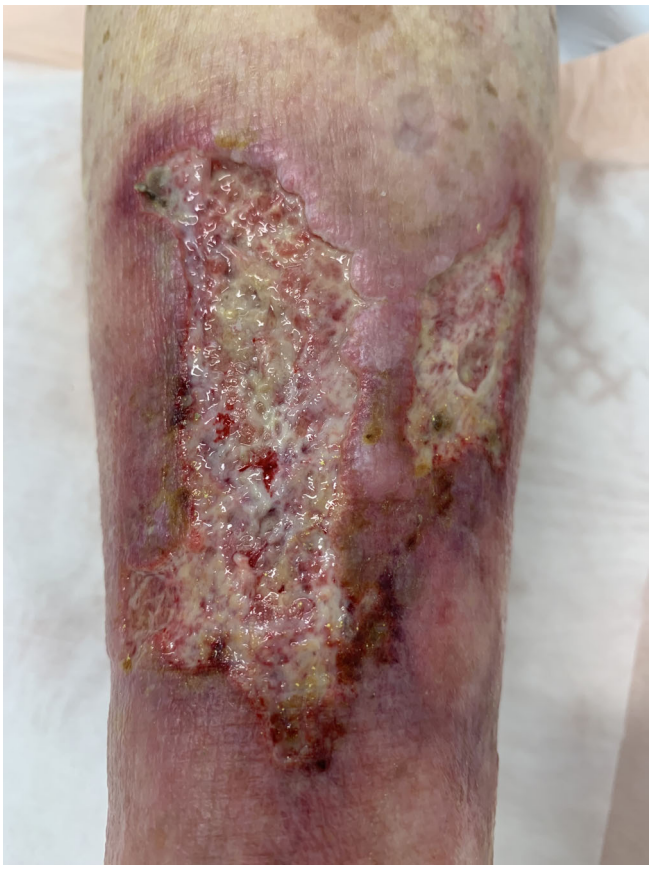

FIGURE 1 *Uremic calciphylaxis leg ulcer: View of right leg on day 0*

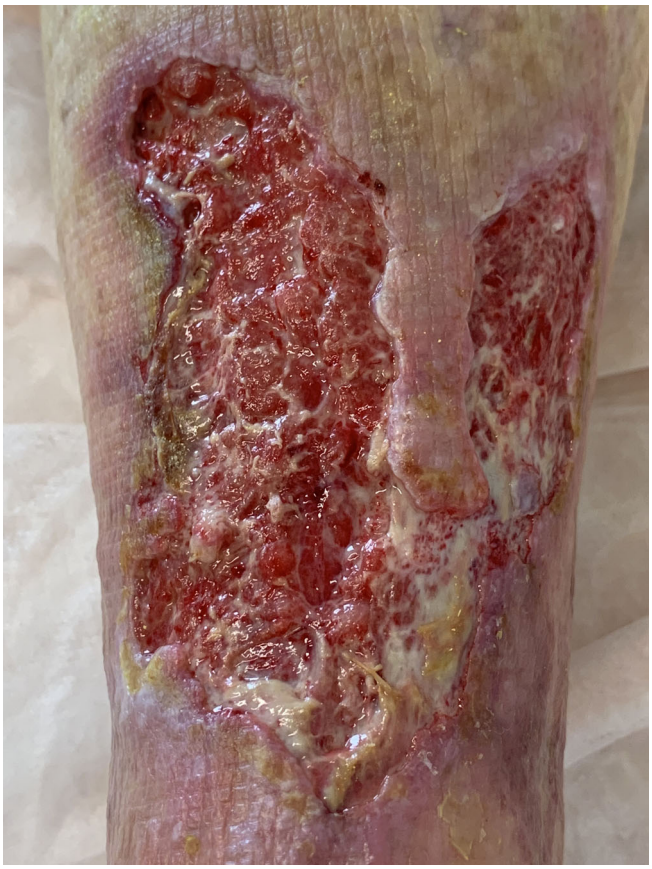

FIGURE 2 Uremic calciphylaxis leg ulcer: View of right leg on day 21 of TCBM treatment

found that over the 3 week treatment, there was some decrease in overall wound size (left: −9%, right: −5%) (photos acquired post debridement), and a much larger increase in granulation tissue in the wound bed (left: 59%, right: 78% of total wound size was granularized on day 21). Two views of her right leg wound on day 0 and day 21 are shown below in Figures 1 and 2, respectively. No adverse reactions, neither local nor systemic, were experienced by the patient.

UC is truly an "orphaned disease" that causes significant suffering and reduced quality of life. In such a chronically ill, complex and compromised patient, one would not expect any level of improvement, yet, marginally reduced wound size and increased granulation tissue occurred, in the very limited treatment duration, that may have continued if she had completed the protocol. Based on our current understanding of the ECS, we theorize that the improvements observed may be due to TCBM acting to dampen the hyper-inflammatory state present in chronic wounds, as well as probably promoting vasodilation of the micro-vasculature within both wound beds and peri-wound tissues. This provokes speculation that TCBM may hold promise as a potential non-invasive treatment option for UC, thus warranting further investigation through controlled clinical trials.

ACKNOWLEDGMENTS

We thank Anna Mann for assistance in literature services.

CONFLICT OF INTEREST

Vincent Maida is President & CEO of VinSan Therapeutics Inc. Other authors do not have any competing interests to declare.

AUTHOR CONTRIBUTIONS

Vincent Maida & Lydia Zomparelli study design; Runjie Bill Shi & Francesco Gabriele Tatangelo Fazzari data analysis; all authors involved in manuscript development.

ETHICS STATEMENT

William Osler Health System REB 18-0038 (Brampton, Ontario, Canada).

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzedanalysed during the current study are available in the ISRCTN registry (Study ID # ISRCTN16488940), https://doi.org/10.1186/ISRCTN16488940. The original photographs used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Vincent Maida[1,2]
Runjie Bill Shi[1]
Francesco Gabriele Tatangelo Fazzari[3]
Lydia Zomparelli[4]

[1]*Faculty of Medicine, University of Toronto, Ontario, Canada*
[2]*Division of Supportive and Palliative Care, William Osler Health System, Toronto, Ontario, Canada*
[3]*Faculty of Medicine, University of Ottawa, Ontario, Canada*
[4]*Faculty of Science, McMaster University, Hamilton, Ontario, Canada*

Correspondence
Vincent Maida, 101 Humber College Boulevard, Toronto, Ontario, Canada, M9V 1R8.
Email: vincent.maida@utoronto.ca

ORCID

Vincent Maida https://orcid.org/0000-0002-8693-0617

REFERENCES

1. Nigwekar SU, Thadhani R, Brandenburg VM. Calciphylaxis. *N Engl J Med*. 2018;378(18):1704-1714. https://doi.org/10.1056/NEJMra1505292.
2. McCarthy JT, El-Azhary RA, Patzelt MT, et al. Survival, risk factors, and effect of treatment in 101 patients with calciphylaxis. *Mayo Clin Proc*. 2016;91(10):1384-1394. https://doi.org/10.1016/j.mayocp.2016.06.025.
3. Udomkarnjananun S, Kongnatthasate K, Praditpornsilpa K, Eiam-Ong S, Jaber BL, Susantitaphong P. Treatment of Calciphylaxis in CKD: a systematic review and meta-analysis. *Kidney Int Rep*. 2019;4(2):231-244. https://doi.org/10.1016/j.ekir.2018.10.002.
4. Maccarrone M, Bab I, Bíró T, et al. Endocannabinoid signaling at the periphery: 50 years after THC. *Trends Pharmacol Sci*. 2015;36(5):277-296. https://doi.org/10.1016/j.tips.2015.02.008.
5. Tóth KF, Ádám D, Bíró T, Oláh A. Cannabinoid signaling in the skin: therapeutic potential of the "c(ut)annabinoid" system. *Molecules*. 2019;24(5):918. https://doi.org/10.3390/molecules24050918.
6. Bíró T, Tóth BI, Haskó G, Paus R, Pacher P. The endocannabinoid system of the skin in health and disease: novel perspectives and therapeutic opportunities. *Trends Pharmacol Sci*. 2009;30(8):411-420. https://doi.org/10.1016/j.tips.2009.05.004.
7. del RC, Millán E, García V, Appendino G, DeMesa J, Muñoz E. The endocannabinoid system of the skin. A potential approach for the treatment of skin disorders. *Biochem Pharmacol*. 2018;157:122-133. https://doi.org/10.1016/j.bcp.2018.08.022.
8. Maida V, Shi RB, Fazzari F, Zomparelli L-M. Topical cannabis-based medicines: a novel paradigm and treatment for non-uremic calciphylaxis leg ulcers: an open label trial. *Int Wound J* 2009;17:1508-1516. https://doi.org/10.1111/iwj.13484.
9. Shi RB, Qiu J, Maida V. Towards algorithm-enabled home wound monitoring with smartphone photography: a hue-saturation-value colour space thresholding technique for wound content tracking. *Int Wound J*. 2019;16(1):211-218. https://doi.org/10.1111/iwj.13011.